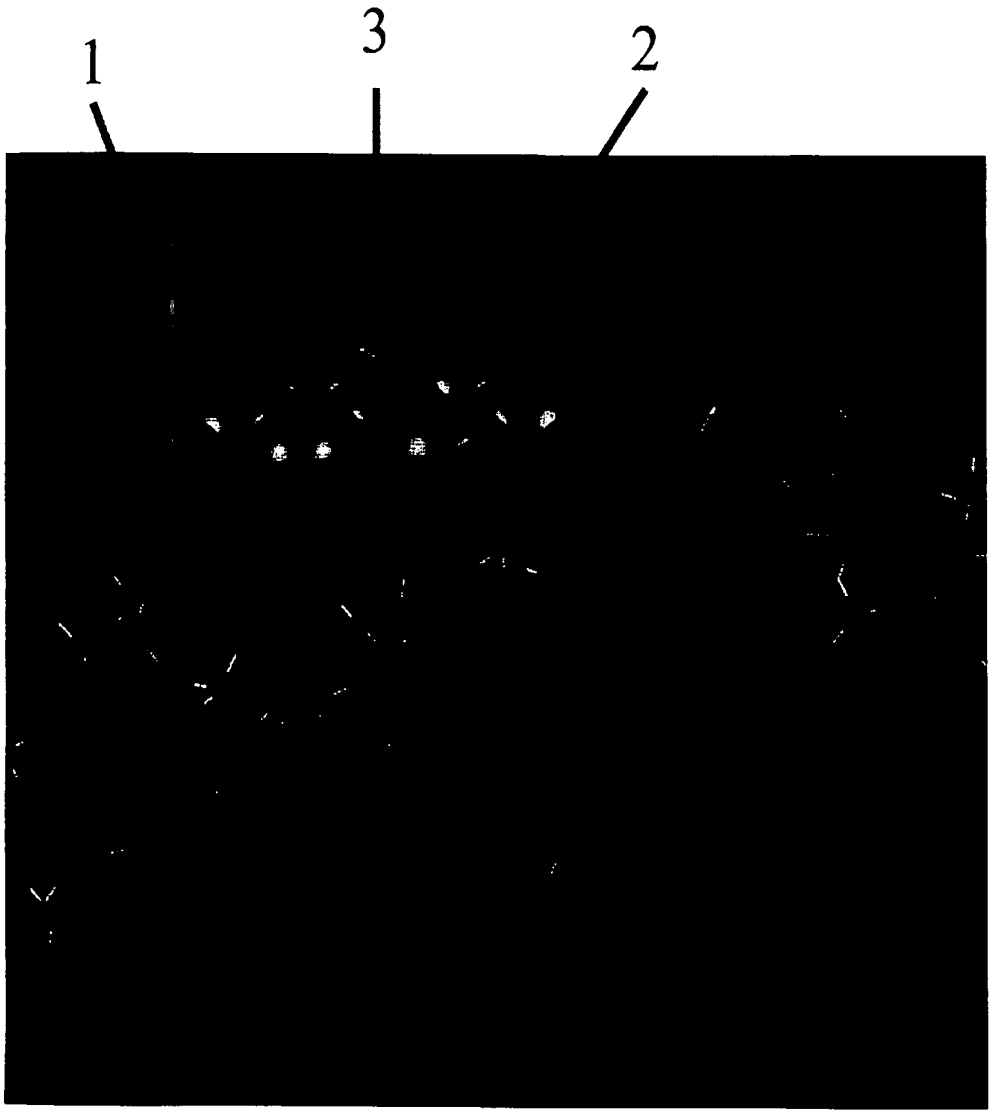
Chemical Approach to Combinatorial Discovery Of β-sheet-Breaking Small Molecules

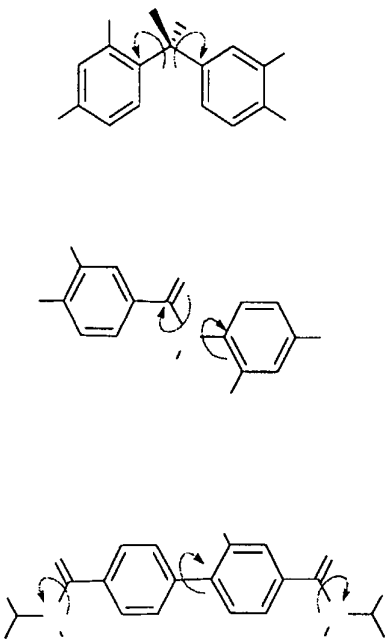


- 1 – Helix stabilization by selective electrostatic interactions
- 2 – Helix stabilization via interaction with the rigid hydrophobic scaffold
- 3 – Combinatorially varied substituents

Figure 1

Title: Methods and Compositions Comprising Non-Peptide Small Molecules That Solublize the Alzheimer's Aβ Peptide Fiber
Applicant: Yves Claude Nicolau and Alexey Eliseev
Docket No.: 54341-0211 (297751)

"Morphomer" concept



- Molecular scaffolds are designed complementary to Aβ helical (soluble) structure
- Conformational restrictions are introduced to partially lock each set of conformations (*morphology*) of library components
- Libraries formed on the basis of scaffolds explore both chemical (Rx) and conformational diversity space

Figure 2

Molecular Adaptation of Morphomers to the Target Leads to Formation of Stronger Complexes

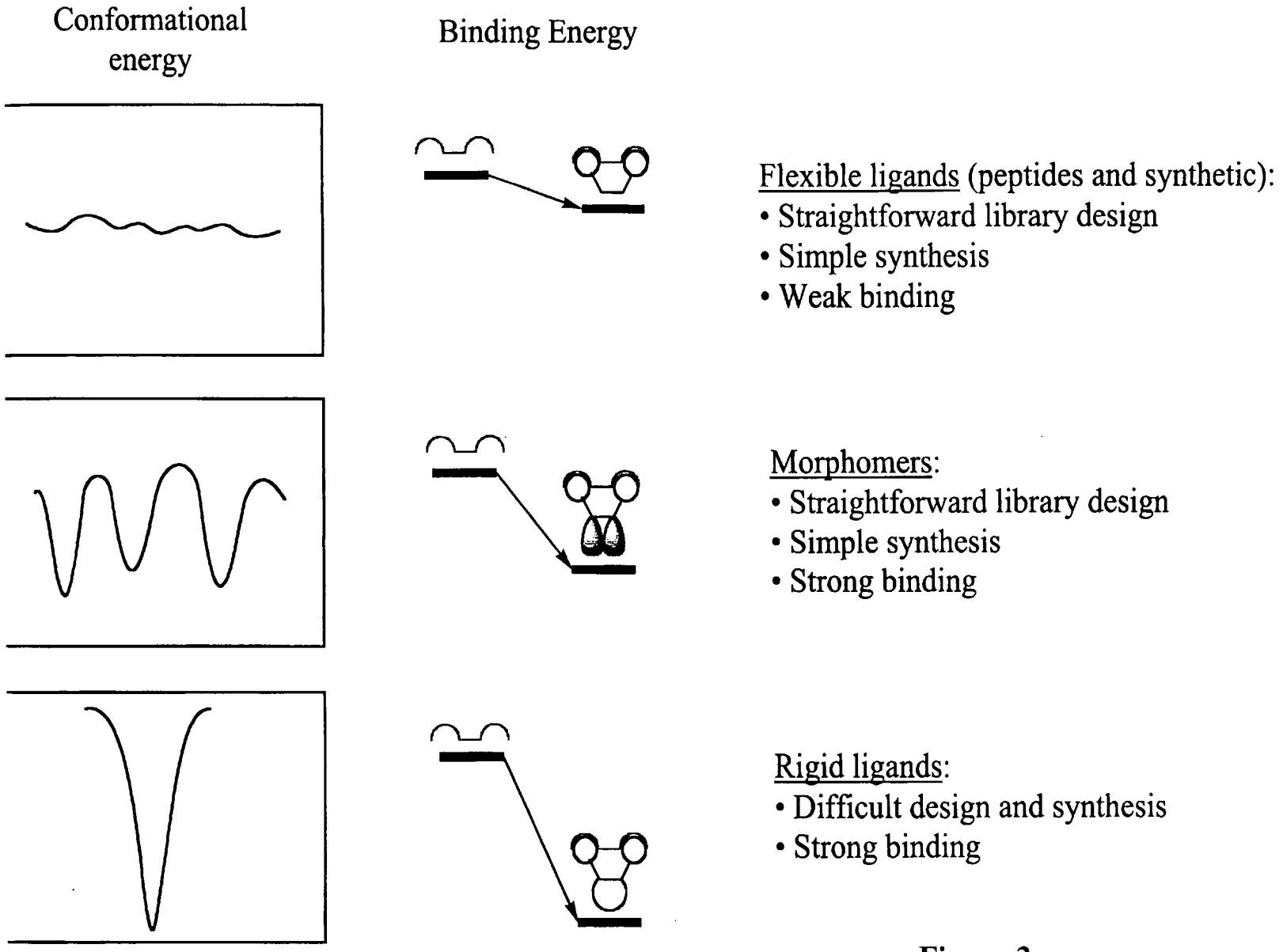


Figure 3

General Strategy of Small Molecules – β-Sheet breakers for Therapy of Alzheimer's Disease

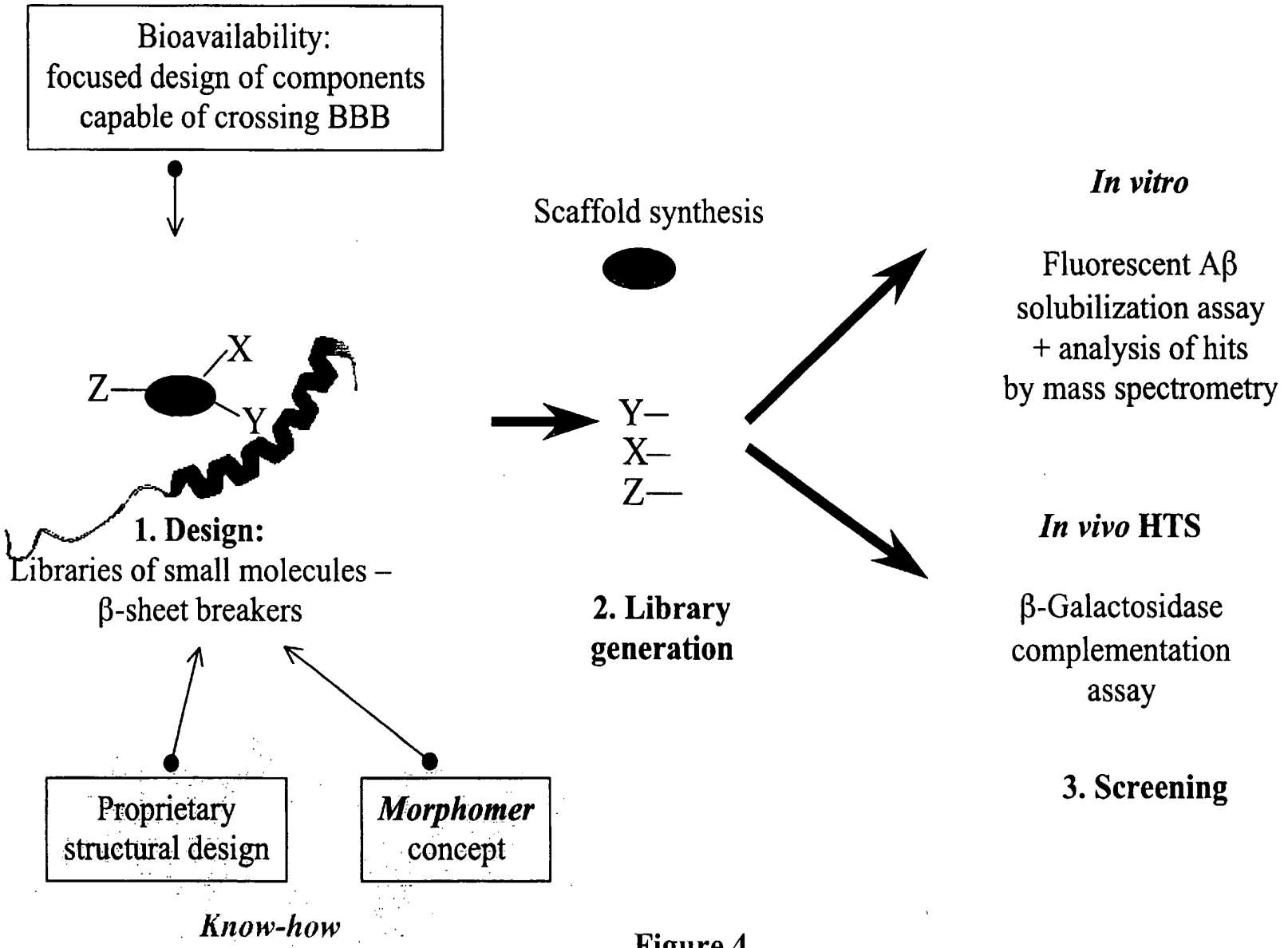


Figure 4

Screening of Small Molecules for Aβ Solubilization Activity

In vitro

- **Fluorescent Assay**:

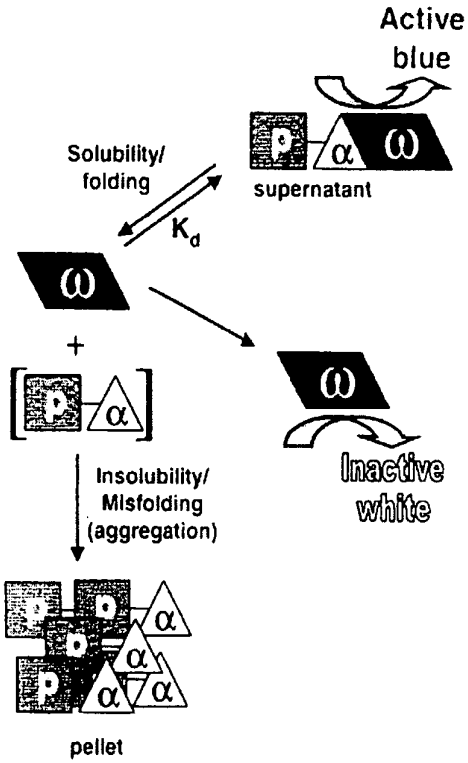
  Aβ fiber stained with Thioflavin T solubilization/depolymerization is monitored by fluorescence decrease

- **Mass spectrometry assay**:

  Complexes of amyloid with small molecules are detected and characterized by MS

  Hits are fully structurally characterized using regiochemical taggig techniques (*provisional patent application filed*)

In vivo



in vivo solubilization assay for Aβ (W.C. Wigley, et al. *Nature Biotechnol.* 2001, *19*, 131-136)

Figure 5